Remarks

The specification and claims have been amended as shown above. Applicant offers the following remarks regarding the Office Action:

Priority claim

Applicant gratefully acknowledges the acceptance of the asserted filing date.

Objection to the Specification

The Office Action stated that incorporation of the reference Int. J. of Phar, 33:201-16 in the specification is improper. Applicant has amended the paragraph from page 12 (page 2 *supra*), the location of the incorporation. The phrase incorporating by reference has been stricken from page 12. Additional salts mentioned in the reference have been added; a copy of the reference is provided at the end of the Remarks. By signature below, the undersigned certifies that no new matter has been added.

Applicant respectfully requests that this ground for rejection be withdrawn.

Claims 12 and 14 Rejection under 35 USC §112, First Paragraph

Applicant appreciates the thorough discussion of this ground for rejection and the difficulty in treating or preventing the elusive metabolic syndrome. In response to the Office Action's rejection on the grounds that prevention of the claimed diseases is not supported, Applicant cancels claims 12 and 14, thus removing the more general term "metabolic disorders of glucose utilization."

Applicant could not find any requirement for 100% prevention (page 5, third full paragraph) in the MPEP or guideline for written description analysis. Applicant therefore questions whether 100% is the accepted standard for rejection. Nevertheless, to advance prosecution, Applicant has cancelled claims 12 and 14 and replaced them with claims 16 and 17.

Applicant believes that this ground for rejection is now moot and should be withdrawn.

Claim 5 Rejection under 35 USC §112, Second Paragraph

This claim was rejected for insufficient antecedent basis in claim 2 for the limitation or alkanoyl-L-carnitine. This was corrected by adding alkanoyl-L-carnitine to claim 2. Now alkanoyl-L-carnitine in claim 5 has an antecedent basis in claim 2.

Applicant believes this ground for rejection is now moot and should be withdrawn.

Rejection under 35 USC §102

Claims 1, 6 and 8 were rejected as being anticipated by Crandall (USPN 6,333,057, December 2001) in light of Saija et al (Int. J. Pharmaceutics, 1998). The Office Action states that Crandall teaches a composition for topical application to the scalp comprising carnitine, coenzyme Q in combination with olive oil. Moreover, Saija indicates that olive oil contains the phenolic compounds oleuropein and hydroxytyrosol.

Crandall does indeed disclose that in the absence of organogels, coenzyme Q is dissolved in a mixture of ethoxydiglycol:ethanol. Then Crandall provides a list of agents, including olive oil, in which to dissolve the preceding mixture. This appears to indicate that olive oil was a minor component of the composition.

Saija et al states that "[h]ydroxytyrosol is more hydrophilic than oleuropein…" (page 131). "[H]ydroxytyrosol is derived by hydrolysis from oleuropein." (page 124) These two compounds at the same concentrations had similar oxidant activity against LA peroxidation (Fig. 2A and 2B, page 128).

Applicant offers two other articles that may shed some light on the differences between the claimed invention and Crandall (with Saija). First, Caruso *et al* (Rapid Evaluation of Phenolic Component Profile and Analysis of Oleuropein Aglycon in Olive Oil by Atmospheric Pressure Chemical Ionization-Mass Spectrometry (ACPI-MS). J Agric Food Chem 2000, 48:1182-1185) explain on page 1182 that during crushing and malaxing (controlled mixing to separate olive oil from the olive paste) processes, hydrolysis of the glycosidic bond occurs and the aglycones pass into the oil while glycosides remain in the waste water. One aglycone that stays in the oil is oleuropein. Because hydroxytyrosol is more hydrophilic (see above) than oleuropein, most of the hydroxytyrosol goes into the waste water. This is illustrated by Table 1 (page 1184) where nine different olive oil samples were tested for various polyphenols. The content of oleuropein for each sample was set at 100%. In comparison, the content of hydroxytyrosol varies from 0 to 12% in one sample; almost half of the samples had no detectable hydroxytyrosol. Thus, olive oil does not contain significant amounts of hydroxytyrosol. As Applicant described in the specification at paragraphs 22 and 23, the hydroxytyrosol is prepared from the waste water. Second, Capasso *et al* ("A Highly Convenient Synthesis of Hydroxytyrosol and Its Recovery from Agricultural Waste Waters." J Agric Food Chem, 1999, 47:1745-48) state that hydroxytyrosol "is the main natural polyphenolic compound occurring in olive oil mill waste waters... and it is also present in virgin olive oil, albeit in *very small amounts* and mainly in the form of natural derivatives" (page 1745) (references omitted and emphasis added).

Thus, because of the minor amount of olive oil in the Crandall composition and the low (or nonexistent) amount of hydroxytyrosol in olive oil, hydroxytyrosol is not present in an effective amount, as claimed and taught in the specification.

Moreover, the Office Action (page 14) states that the Crandall "reference fails to teach (i) the use of acetyl-L-carnitine or an additional carnitine component or pharmacologically acceptable salts thereof..."

Even if Crandall did teach the various carnitines claimed by Applicant, there is no significant hydroxytyrosol in olive oil and only a minor amount of olive oil in Crandall's formulation, failing to enable the combination of carnitine with an effective amounts of hydroxytyrosol. Therefore, Applicant respectfully requests that this rejection be withdrawn.

Rejection of claims 1-6 and 8 under 35 USC §103

I. The Office Action rejected claims 1-6 and 8 as unpatentable over Crandall in light of Saija (cited to show a fact) and further in view of Cavazza WO 00/11968; 2000) and Shug (USPN 5,240,961; 1993).

The Office Action also states that the use of a variety of carnitine compounds (Crandall, 3:48-51) must be capable of improving fatty acid metabolism by stimulation of cardiolipin, which affects the activity of the inner mitochondrial membrane, affecting its permeability and function for proton transport. Then the Office action cited Cavazza for the teaching that carnitines such as those specifically disclosed in the reference also produce energy in the mitochondria by fatty acid oxidation, reactivates mitochondria and restores normal cardiolipin concentrations in the mitochondria. The Office Action states that given the composition of Crandall and the other carnitines disclosed by Cavazza, one would have been motivated to use the broader group of carnitines disclosed in Cavazza, particularly since the combination may have potentiated the mitochondrial effects. The Office Action also indicated that optimizing the ratio or percentages is not patentable when the general conditions of a claim are disclosed in the prior art.

Applicant would like to point out that most of the experiments showed no synergistic effect for multiple carnitines, just some modest increases or decreases. The important factor was the combination of carnitines with lipoic acid. Therefore, Cavazza does not teach or suggest that the combination of carnitines is desirable.

The Office Action (page 14) stated that there are differences between the Crandall reference and the presently claimed subject matter, in that the "reference fails to teach (i) the use of acetyl-L-carnitine or an additional carnitine component or pharmacologically acceptable salts thereof…" In addition, Applicant believes that the Crandall and Saija references cannot be the basis for an obviousness rejection for the reasons discussed above.

Taking into account the lack of hydroxytyrosol in all three references and the limited disclosure of carnitines in Crandall and the lack of synergy in Cavazza, Applicant avers that a *prima facie* case of obviousness has not been made and the rejection should be withdraw.

A Shug reference was mentioned in the opening paragraph of the obviousness rejection; however, its contribution to the rejection did not appear to be discussed. Applicant would not like to speculate at this time as to the disclosure the Office Action would like to attribute to Shug and looks forward to being fully apprised of the extent of its applicability. In the mean time, Applicant requests that the rejection be withdrawn.

II. Claims 1-15 were rejected under 35 USC 103(a) as unpatentable over Cavazza (USPN 6,365,622; 2002) or Cavazza (WO 11968; 2000), in view of Saija et al. The Office Action stated that Cavazza teaches a composition in many pharmaceutical forms but fails to teach the use of a mixture of carnitine with polyphenols containing hydroxytyrosol. Cavazza teaches neither a mixture of polyphenols nor hydroxytyrosol. However, the Office Action stated that Cavazza teaches carnitine combinations with an antioxidant (lipoic acid), which could be substituted with hydroxytyrosol in a polyphenolic mixture both of which are antioxidants, as taught by Saija.

In contrast, Saija tested only pure hydroxytyrosol and oleuropein. The Saija reference does not teach or suggest hydroxytyrosol in a mixture of polyphenols to improve the antioxidant status. Moreover, Cavazza does not teach an improvement with a mixture of carnitines, as is claimed. Therefore, Cavazza does not support a rejection of claims providing a variety of carnitines; Cavazza showed only modest differences between one carnitine and multiple carnitines, which would not suggest making further combinations. Thus, the combination does not render obvious claims to a carnitine and hydroxytyrosol in polyphenols.

Therefore, Applicant believes that a *prima facie* case of obviousness has not been proved and requests that the rejection be withdrawn.

Judicially Created Obviousness Double Patenting

The Office Action stated that the claims are obvious over the inventor's four prior patents (6197308; 6416808; 6165475 and 6936287). However, none of these patents teach or suggest combining carnitine with hydroxytyrosol in a mixture of polyphenols nor treatments therewith. Therefore, Applicant requests that this rejection be withdrawn.

In addition, the Office Action provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims of 10/190,043 in view of Cavazza (USPN 6365622; 2002). In contrast, as Applicant noted above, Cavazza teaches little or no improvement with a mixture of carnitines over a single carnitine; consequently, one would not be motivated to make other combinations. The 10/190,043 application does not teach a combination of hydroxytyrosol with carnitines. Therefore, the combination of references fails to teach or suggest the claimed combination of methods of treatment. Applicant requests that this rejection be withdrawn.

CONCLUSION

Applicant believes that all grounds for rejection have been addressed and overcome. A notice of allowance is respectfully requested. If it would further the prosecution of this application or there is a need for any clarification, the Examiner is requested to telephone the undersigned to reach agreement and disposal of this case.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as Express Mail No. EQ199368175US, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 12th day of June, 2006.

Barbara J. Luther
Name

Barbara J. Luther
Signature